Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

MCM3 (minichromosome maintenance complex component 3)

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Published in Atlas Database: October 2014
Online updated version : http://AtlasGeneticsOncology.org/Genes/MCM3ID41319ch6p12.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/62479/10-2014-MCM3ID41319ch6p12.pdf
DOI: 10.4267/2042/62479

Abstract

Review on MCM3, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: HCC5, P1-MCM3, P1.h, RLFB

HGNC (Hugo): MCM3

Location: 6p12.2

DNA/RNA

Description

The human MCM3 gene is located on the minus strand and spans 20868 bps of genomic region (52264014-52284881). This gene has 7 transcripts (splice variants). It has 853 amino acids and its size is about 91 kDa. It contains a nuclear localization signal and possess an ATPase/helicase region at the centre. It has a total of 17 exons and extends a bit more than 20 KB of genomic DNA. (Hofmann et al., 2000) (Fig. 1).

Transcription

There are two transcript variants encoding different isoforms known for MCM3. These are transcript variant 1 (accession number NM_002388.4) and transcript variant 2 (NM_001270472.1). The transcript variant 2 lacks an alternate exon compared to transcript variant 1. MCM3 gene has been observed to be expressed highly in different cancer cell lines as compared to normal tissues (Ha et al., 2004). Higher mRNA expression of MCM3 was also shown to be linked with papillary thyroid carcinoma (PTC) (Igci et al., 2014). The expression level of MCM3 is also increased in cell lines overexpressing E2F, suggesting that MCM3 is also target of E2F (Leone et al., 1998; Bruemmer et al., 2003).

Pseudogene

There is no known pseudogene for MCM3.

Protein

Description

The protein encoded by MCM3 gene is known to be a well conserved mini-chromosome maintenance protein (MCM) which is needed for triggering the eukaryotic genome replication.
It acts as DNA replication licensing factor.
The well known other synonym for this protein is DNA polymerase alpha holoenzyme-associated protein P1 due to its indispensable role in DNA replication and cell proliferation and also participates in the control of genome duplication during cell cycle. The MCM3 protein is composed of 808 amino acid residues, having molecular mass of approximately 91 kDa and a basal isoelectric point of 5.53.The MCM3 protein is subunit of the protein complex (MCM 2-7) i.e the minichromosome maintenance (MCM) complex. It contains active ATPase sites which supplement to the helicase activity needed during DNA replication. MCM3 protein contains 8 nucleotide length region that binds nucleotide phosphates. (Fig. 2).
MCM3AP (Minichromosome Maintenance-3 Associated Protein) interacts and acetylates MCM3 protein inhibiting cell cycle progression.

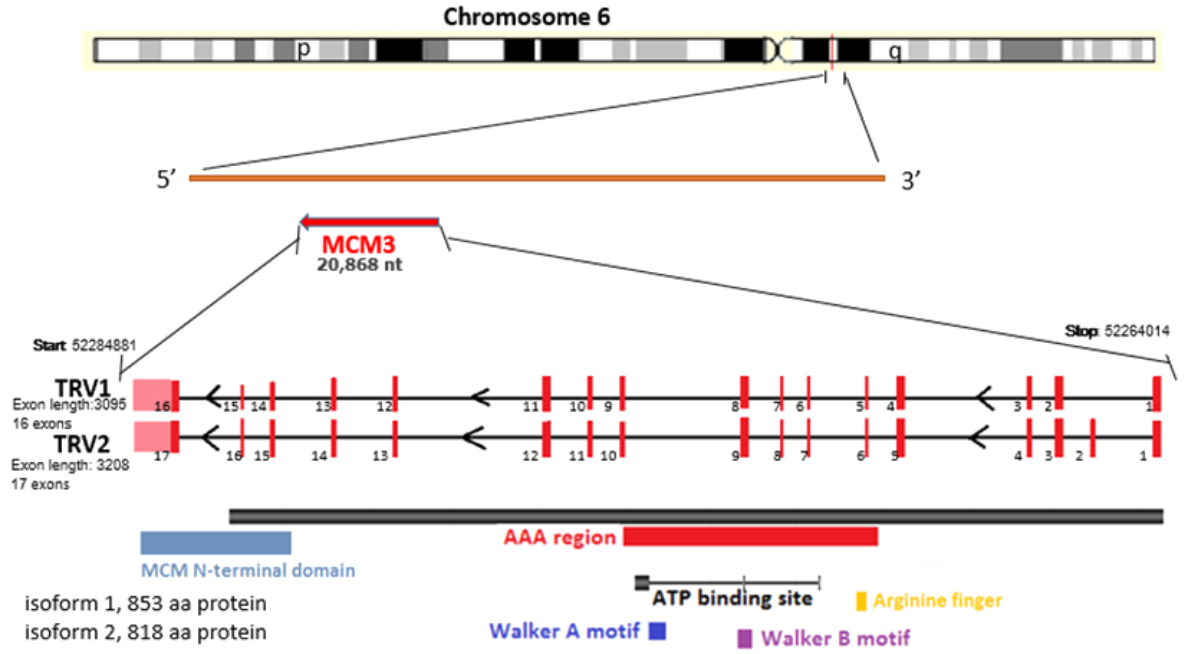

Figure 1. MCM3 gene location, the representation of two major splice variants, and the depiction of major motifs.

There is an interaction between MCM3 and MCM3AP which is required for nuclear localization and chromatin binding of MCM3AP (Takei et al., 2002). The acetylase activity of MCM3AP is known to inhibit only initiation of DNA replication and does not inhibit its elongation (Takei et al., 2002). MCM3 are known to have distinguishable nuclear localization sequences (NLS), indicating that these MCMs help in providing nuclear targeting to different other members of the MCM family (Kimura et al., 1996; Forsburg, 2004).

Like other MCM proteins, MCM3 is a member of the AAA+ class of ATPases. It contains binding site for ATP, Walker A motif, Walker B motif and arginine motif. AAA+ ATPases usually form ATP-dependent complexes usually heterohexamers. The structure of MCM3 includes the MCM box spanning about 200 residues. This peculiar MCM box has two ATPase consensus domains or motifs. One of them is the Walker A domain which includes the active site with P-loop. In Walker A consensus, glycine is replaced by alanine or serine along with many other conserved residues, eventually forming the MCM-specific region GDPxx(S/A)KS (Forsburg, 2004). Other is the classic Walker B which is hydrophobic in nature that is primarily responsible for the hydrolysis of ATP rather than binding. Like all the MCM proteins, the Walker B motif of MCM3 possess the conserved sequence IDEFDKM that distinguishes the MCM family. There is also presence of a short motif, SRFD that is present about 70 residues following the Walker B element, constitutes an "arginine finger". Infact all other MCMs also contain these sequences.

The MCM3 also possesses a zinc finger residing prior to the MCM box that somewhat matches a classic zinc finger region, but has been stated that the residues are capable of chelating zinc (Fletcher et al., 2003).

Biochemical analysis also revealed that the zinc motif aids in formation of complex assembly as well as ATPase activity (Poplawski et al., 2001; Fletcher et al., 2003). Members of the AAA+ ATPases are well known to function as molecular chaperons. The AAA+ proteins possess several distinct characteristics. The formation of active ATPase sites in the MCM2-7 ring takes place via interacting surfaces of two adjacent subunits. This interaction occurs in such a way that the conserved arginine finger motif resides in trans relative to the Walker A box (ATP-binding site) of the of the adjacent subunit.

Expression

Despite an increase in transcription for some MCM genes during the G1/S phase in dividing cells, MCM3 protein levels remain constant during the cell cycle (Forsburg et al., 1997; Diffley and Labib, 2002). MCM3 protein is found to have nuclear expression in all in proliferating cells. There is high expression of MCM3 proteins in trophoblastic cells of placenta, hematopoietic cells of bone marrow. But it has not been detected in decidual cells of placenta, brain, liver, kidney, ovary, spleen, lung, skeletal muscles, smooth muscles and heart muscles.

MAGTVVLDDVELREAQRDYLDFLDDEEDQGIYQSKVRELISDNQYRLIVNVNDLRRKNEKRANRLLNNA
FEELVAFQRALKDFVASIDATYAKQYEEFYVGLEGSFGSKHVSPRTLTSCFLSCVVCVEGIVTKCSLVR
PKVVRSVHYCPATKKTIERRYSDLTTLVAFPSSSVYPTKDEENNPLETEYGLSVYKDHQTITIQEMPEK
APAGQLPRSVDVILDDDLVDKAKPGDRVQVVGTYRCLPGKKGGYTSGTFRTVLIACNVKQMSKDAQPSF
SAEDIAKIKKFSKTRSKDIFDQLAKSLAPSIHGHDYVKKAILCLLLGGVERDLENGSHIRGDINILLIG
DPSVAKSQLLRYVLCTAPRAIPTTGRGSSGVGLTAAVTTDQETGERRLEAGAMVLADRGVVCIDEFDKM
SDMDRTAIHEVMEQGRVTIAKAGIHARLNARCSVLAAANPVYGRYDQYKTPMENIGLQDSLLSRFDLLF
IMLDQMDPEQDREISDHVLRMHRYRAPGEQDGDAMPLGSAVDILATDDPNFSQEDQQDTQIYEKHDNLL
HGTKKKKEKMVSAAFMKKYIHVAKIIKPVLTQESATYIAEEYSRLRSQDSMSSDTARTSPVTARTLETL
IRLATAHAKARMSKTVDLQDAEEAVELVQYAYFKKVLEKEKKRKKRSEDESETEDEEEKSQEDQEQKRK
RRKTRQPDAKDGDSYDPYDFSDTEEEMPQVHTPKTADSQETKESQKVELSESRLKAFKVALLDVFREAH

Figure 2. MCM3 protein sequence showing AAA region (blue coloured), ATP binding site (blue colour underlined), Walker A motif (highlighted with yellow color), Walker B motif (highlighted with grey color), SRFD arginine finger motif (red).

This DNA replication licensing factor is also expressed at lower intensity in many other cell types, including squamous epithelial cells of oesophagus, glandular cells of appendix and breast, urothelial cells of the urinary bladder, respiratory epithelial cells of nasopharynx.

Localisation

The MCM3 protein is localized to the nucleus.

Function

MCM3 protein is extremely conserved mini-chromosome maintenance proteins (MCM) in eukaryotes and is ubiquitously expressed. MCM3 is one of the members of MCM family with chromatin-binding proteins. MCM3 by acting as an indispensable factor permits a single round of replication of DNA per cell cycle. It is responsible for the initiation of eukaryotic genome replication and cell proliferation and monitors the cell cycle control of genome duplication. MCM3 gene encodes P1 protein which has a role in the DNA replication process.

MCM3 protein is part of the protein complex consisting of MCM2-7. It participates in the formation of the heterohexameric MCM complex, which is loaded onto the chromatin at sites of DNA replication, leading to the formation of pre-replication complex (pre-RC). The proteins that compose the MCM complex also serve as DNA helicases that unwind the DNA double helix at the replication forks apart from the initiation of replication. Furthermore, MCM3 actively participates in cell cycle regulation. The MCM3 is responsible for genome stability, as it limits the replication to only once per cell cycle.

MCMs have a direct role in transcription. There are several evidences suggesting that the MCM proteins do associate with specific transcription factors. Mcm3-Mcm5 complex forms a heterodimer associating with STAT1a (a transcription factor) during biochemical purification (Zhang et al., 1998; DaFonseca et al., 2001). Infact MCM5 mediates this association. MCM3, MCM2 and MCM5 form the peripheral subunits of the complex that is known to negatively regulate the active MCM core subunits (MCM4, MCM6 and MCM7). It is known to interact directly with MCM5/CDC46. The well known MCM3 acetylating protein, MCM3AP (a chromatin-associated acetyltransferase) binds and acetylates MCM3 further inhibiting the initiation of DNA replication including cell cycle progression.

It has been shown that there is a functional interaction between two important moieties i.e the glucocorticoid receptor and GANP (germinal center-associated protein)/MCM3AP. GANP and MCM3AP are known to bind to the MCM3 protein which is involved in triggering of DNA replication (Osman et al., 2006). It is shown that cyclin E/Cdk2 phosphorylates MCM3 at a particular site i.e Thr722, regulating the loading of MCM3 onto chromatin and thus controls S phase checkpoint (Li et al., 2011). Mcm3, Mcm2 and Mcm4 show cell cycle specific phosphorylation that relates to chromatin binding. They are shown to be hypophosphorylated and chromatin-bound in G1 which eventually gets phosphorylated by Cdk activity at G1/S and later in the cell cycle (Fujita et al., 1998). Phosphorylation of Mcm proteins is also needed for pre-RC assembly and activation which is dependent on Cdk activity and Cdc7-Dbf4 kinase is also required (Sato et al., 1997; Weinreich and Stillman, 1999; Masai et al., 2000). In summary, the molecular function of MCM3 includes DNA helicase activity, DNA binding, protein binding and ATP binding while the biological processes of MCM3 includes DNA replication initiation, DNA strand elongation, mitotic cell cycle, DNA replication, DNA duplex unwinding, G1/S transition during mitotic cell cycle.

Homology

The gene encoding the human P1 protein (MCM3) has 60% homology to the yeast MCM3 (minichromosome maintenance deficiency) replication control gene of S. cerevisiae (Thommes et al., 1992). In another study it has been observed that MCM3 shares three central regions of high

sequence similarity i.e about 75% as well as highly hydrophilic carboxy-terminal region with the Mcm3 replication protein of the yeast (Schulte et al., 1995). MCM3 is also homologous to other MCM complex components (MCM2, MCM5, MCM6, MCM7) and can form several kind of heteromeric complexes. Mutants defective in MCM2 or MCM3 are extremely similar in phenotype. They both possess an autonomously replicating sequence (ARS)-specific minichromosome maintenance defect, however their ARS specificities are not identical. MCM3 resembles MCM2 as they both contain NLS (Nuclear localization sequences) and are involved in translocating the complex from the cytoplasm to the nucleus (Gozuacik et al., 2003).

Mutations

A nuclear localization signal of human MCM3 has been clarified and being established that mutagenesis on the nuclear localization signal of MCM3 affects the binding of newly isolated MCM3-assosiated protein, Map80 (Takei and Tsujimoto, 1998). In Saccharomyces cerevisiae, two mutant alleles i.e mcm3-1 and mcm3-10 that are defective at different steps of the replication initiation process have been characterized (Lei et al., 2002). Both Mcm3-10 and Mcm3-1 have defectiveness with regard to the recruitment of the MCM2-7 complex to replication origins. Mcm3-10 affects a step before, and Mcm3-1 affects a step after the recruitment of the MCM2-7 complex to replication origins. Mcm3-1 has a G246E mutation that lessens the efficiency of replication initiation (Yan et al., 1993).

Implicated in

Uterine cervical cancer

It has been shown that MCM3 is ubiquitously expressed in cancer cells by immunohistochemical studies of surgical materials from human uterine. Moreover, cancerous cells has higher MCM3 expression than in normal proliferating cells of the uterine cervix and dysplastic cells, making it a useful marker to differentiate these cells (Ishimi et al., 2003). These results indicate that the malignant transformation of cells is directly related to the higher expression of MCM3 protein.

Papillary thyroid carcinoma

Papillary thyroid carcinoma (PTC) is known to be the most common histological type among the other types which accounts for up to 80 % of the total thyroid cancer cases (Fagin and Mitsiades, 2008). It has been shown that the MCM3 protein expression levels were overexpressed in papillary thyroid as compared to normal thyroid tissues through immunohistochemical analysis and Western blot analysis (Lee et al., 2010). A comparative study of MCM3 protein expression levels was also done in follicular variant of papillary thyroid carcinoma (FVPTC), classic variant of papillary thyroid carcinoma (CVPTC), and multi-nodular goitre (MNG) tissues. MCM3 protein expression was higher in FVPTC and CVPTC as compared to MNG (Igci et al., 2011; Igci et al., 2014). This shows that MCM3 might be used as a suitable marker in order to distinguish FVPTC and CVPTC from MNG.

Brain malignancies

MCM3 shows a restricted immune response by cancer in patients with brain malignancies. It is a strong predictor of survival in patients with anaplastic astrocytoma (Soling et al., 2005). MCM3 has been shown to have higher expression in human astrocytic tumors and highlights a cancer-restricted humoral immune response in patients with brain tumors and brain metastases but not in healthy controls. MCM3 expression in diffuse astrocytoma is found to be significantly associated with age, histologic grade, time to recurrence (Soling et al., 2005).

Endometrial carcinogenesis

The expression of MCM3 in endometrial carcinomas was shown to be significantly lower than the normal proliferative endometrium. The expression of MCM3 also differs according to the phases. It is significantly higher in the proliferative phase than in the secretory phase. The above observations show that the expression of MCM3 reflects cell proliferation in normal and hyperplastic endometria (Kato et al., 2003). The replication-licensing system may be aberrant in endometrial carcinomas as there is an inconsistency between the expression of MCMs and cell proliferation in endometrial carcinomas.

Salivary gland tumors

MCM3 was significantly higher in mucoepidermoid carcinomas (MEC) and adenoid cystic carcinomas (ADCC) with respect to pleomorphic adenomas (PA). A high sensitivity and specificity for MCM3 was obtained to differentiate benign and malignant tumors (Ashkavandi et al., 2013).

Other malignancies

Minichromosome maintenance 3 (MCM3) gene was highly expressed in a lot of human cancers, like lymphoma, leukemia, carcinomas of the uterine cervix, stomach, breast, kidney and lung, malignant melanoma as well as benign and malignant melanocytic skin lesions (Ha et al., 2004; Gambichler et al., 2009). MCM3 protein was also found to be upraised in several human cancer

tissues analysed by western blot and immunohistochemical analyses (Ha et al., 2004).

To be noted

Acknowledgments: Kaifee Arman is recipient of Graduate Scholarship from TUBITAK under the program 2215-Graduate Scholarship Program for International Students.

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This article should be referenced as such:

Arman K, Bozgeyik E, Igci YZ. MCM3 (minichromosome maintenance complex component 3). Atlas Genet Cytogenet Oncol Haematol. 2015; 19(10):611-616.